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A Practical Synthesis of Enantiomerically Pure *N*-Benzyl-α-methyl Benzylamine

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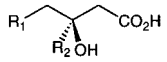
Abstract:

Optically pure *(R)*- and *(S)*-*N*-benzyl-α-methyl benzylamine have been prepared on pilot plant scale from benzaldehyde and α-phenyl-ethylamine via palladium-catalyzed hydrogenation of the intermediate (*R*)-benzylidene-(1-phenylethyl)amine.

Introduction

Despite recent advances in asymmetric catalysis, classical resolution remains prevalent in cost-driven industrial processes. There are several enantiomerically pure, commercially available amines that can be used for this purpose; however, their cost frequently limits their use on an industrial scale. Our work on the synthesis of improved HIV protease inhibitors required a method for the synthesis of β-hydroxy carboxylic acids of structure **1**. While screening a range of chiral amines for the classical resolution of these substrates, it became apparent that *N*-benzyl-α-methyl benzylamine[1] (**3**) proved superior both in terms of yield and % ee of the final material. The high commercial cost of this amine, however, prevented its practical use on increased scale. To make the project cost-effective, we decided to synthesize this compound in-house.



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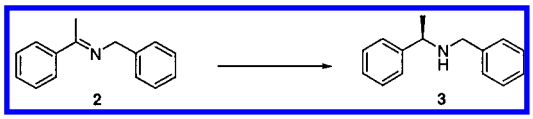
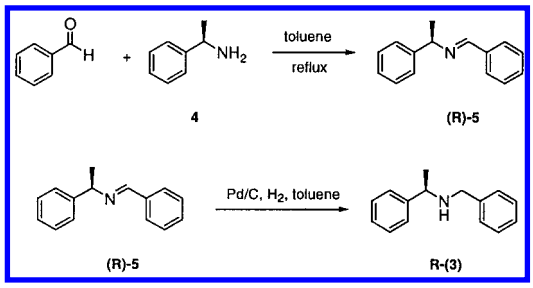
Enantiomerically pure *N*-benzyl-α-methyl benzylamine has found range of utility in addition to its use as a resolving agent. The lithium amide derived from the amine has been used for asymmetric deprotonations of prochiral ketones used in stereoselective aldol reactions.[2] The lithium and magnesium amides have been used successfully in asymmetric Michael additions.[3]

A review of the literature revealed that this amine can be made via the asymmetric hydrogenation of imine **2** using either optically active zirconocene[4] or iridium complexes,[5] but these methods only provide material in 76 and 90% ee, respectively. The amine was also prepared by the monoalkylation of 1-phenylethylamine with benzyl bromide but required large amounts of DMPU as the solvent.[6] Another paper[7] describes the use of $NaBH_3CN$ to reduce the imine **5**; unfortunately the yields are low (60%), and some racemization cannot be avoided even with careful pH adjustment. Our goal was to develop a high-throughput process that would yield enantiomerically pure material on a consistent basis. Herein we report an inexpensive synthesis of *(R)*- and *(S)*-*N*-benzyl-α-methyl benzylamine starting with readily available *(R)*- and *(S)*-α-phenylethylamine.

Scheme 1



Scheme 2



Results and Discussion

The formation of the imine **(R)-5** in both benzene and methylene chloride solvents has been previously reported.[8] After surveying a number of more EPA-friendly solvents, we report that the imine formation occurs readily in toluene, and despite the increased temperature required to remove the water, no racemization is observed.

Debenzylation of the product during the reduction of the imine was a serious concern since this could contaminate the product with both benzylamine and α-phenylethylamine. The presence of these impurities understandably diminishes the efficiency of the subsequent resolution. Of the catalysts screened, 5% Pd/C caused the least hydrogenolysis. We also observed that debenzylation was suppressed to a greater extent at higher hydrogen pressures, which is counterintuitive, but consistent with the observation that hydrogenolysis is generally a "hydrogen-starved" process. Because of equipment capabilities, we ran these reactions at 50 psig hydrogen. If the reaction was run for substantially longer than the usual

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(1) The amine **3** has been used successfully as a resolving agent. (a) Juaristi, E. *Tetrahedron Asymmetry* **1998**, *9*, 715. (b) See also: Japanese Patent JP 05255180A, 1993.

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(5) Tani, K.; Onouchi. J.; Yamagata, T.; Kataoka, Y. *Chem. Lett.* **1995**, 955.

(6) Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, *12*, 1243−6.

(7) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523.

(8) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 7(11), 2795. (b) Bourzat, J. D.; Comercon, A. *Tetrahedron Lett.*, **1993** *34*, 6049.

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30 min, debenzylation was observed. The reaction kinetics under these conditions, however, proved to be such that the reduction greatly outpaced hydrogenolysis.

This procedure produces material of >95% overall purity in a consistent manner and can be run at the scale shown in one 8-h shift. No racemization is observed, and the final ee is the same as that of the initial α-phenethylamine. The only significant impurity is benzyl alcohol, which can be removed with further distillation, if desired, to give material of 99% purity. Importantly, this process also minimizes solvent, eliminates some hazardous materials, and produces consistent low-cost material.

Experimental Section

General Methods. Reagents and solvents were commercial and used as received. ^{1}H NMR was recorded at 200 MHz.

***(R)*-Benzylidene-(1-phenylethyl)amine. *(R)*-5.** *(R)*-α-phenylethylamine (98.8% ee, 31 kg, 256 mol), toluene (260 L),[9] and benzaldehyde (29 kg, 273 mol) were combined at ambient temperature. The solution was heated to reflux. Water was removed in a water separator (approximately 2 h). The reaction solution was cooled to 20 °C. The imine **(R)-5** was not isolated and was carried into the hydrogenation reaction.

***(R)*-*N*-Benzyl-α-methyl Benzylamine. (R)-3.** The solution containing **(R)-5** was charged to a reactor containing 50% water−wet 5% palladium on carbon (4.8 kg). The reactor was pressurized with hydrogen to 50 psig, and the reaction was hydrogenated at 20 °C. The maximum temperature reached during the hydrogenation was 25 °C. The reaction was continued until no more hydrogen uptake was observed (about 30 min). The solution was filtered to remove the palladium catalyst and concentrated in vacuo to afford a yellow oil (52.9 kg, 97.8%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36−7.22 (m, 10H), δ 3.78 (q, 1H, J = 7 Hz), δ 3.63 (d, 1H, J = 15 Hz), δ 3.61 (d, 1H, J = 15 Hz), δ 1.35 (d, 3H, J = 7 Hz); Chiral HPLC[10] 99.4% *R* : 0.6% *S*; Anal. Calcd. for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.4%; H, 8.0%; N, 6.58%.

***(S)*-*N*-Benzyl-α-methyl Benzylamine. (S)-3. (S)-3** was prepared as described above in the preparation of **(R)-3** using *(S)*-α-phenylethylamine. The **(S)-3** synthesis was carried out on the same scale.

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(9) The formation of the imine **R-5** and the hydrogenation to give **R-3** have been run at double this concentration at the 20 gm scale. Furthermore, water was not removed from the reaction prior to hydrogenation. The reaction behaved identically.

(10) Chiracel OD-H column (250 × 4.6 mm), 1000:20:1 (hexane:iPrOH:Et_2NH); 0.5 mL per minute, 254 nm. Elution time: 14.5 min. *(R)*, 15.8 min. *(S)*.